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Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

When and How to Stop Dual Antiplatelet Therapy After PCI

By Jeffrey Zimmet, MD, PhD

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Dr. Zimmet reports no financial relationships relevant to this field of study.

SYNOPSIS: Among patients with high-risk percutaneous coronary intervention who had completed three months of dual antiplatelet therapy with ticagrelor, patients who were randomized to ticagrelor alone experienced similar ischemic outcomes and a lower risk of bleeding at one year compared with those maintained on ticagrelor and aspirin.

SOURCE: Mehran R, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 2019; Sep 26. doi: 10.1056/NEJMoa1908419. [Epub ahead of print].

The optimal duration of dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) has been the subject of intense study and debate for years now. Longer DAPT duration has been demonstrated to reduce the chances for ischemic outcomes at the expense of an increase in clinically relevant bleeding. In most cases, the completion of DAPT has meant paring down to single antiplatelet therapy with aspirin alone. Most clinical trials studying shortened DAPT duration have followed this paradigm. However, more recently, trials have taken the opposite approach, shortening the duration of DAPT by withdrawing aspirin, leaving the P2Y12 inhibitor for a longer course.

The authors of TWILIGHT, the most recent entry in this space, sought to enroll patients after PCI who had clinical and angiographic features associated with elevated risk for ischemic and bleeding events. In this multinational trial involving 187 sites in 11 countries, Mehran et el enrolled 9,006 patients in the direct post-PCI period. Of these, 7,119 were randomized after completing three months of DAPT with aspirin and ticagrelor, with the remainder excluded due to issues including nonadherence to DAPT (the majority), adverse clinical events during the three months post-PCI, and withdrawal of consent or failure to follow up. Ultimately, 3,564 patients were randomized to continue ticagrelor plus aspirin to complete 12 months of therapy, while

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the remaining 3,555 received ticagrelor and placebo. Randomized patients were a mean age of 65 years, 36.8% were diabetic, 23.8% were female, and 64.8% had undergone PCI for acute coronary syndrome (a combination of NSTEMI and unstable angina; STEMI patients were excluded specifically).

At one year, patients who continued on ticagrelor monotherapy had a lower incidence of the primary endpoint of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding (4.0% vs. 7.1%; hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.45-0.68; $P < 0.001$). Incidence of more serious BARC types 3 and 5 bleeding also was significantly lower in the ticagrelor monotherapy group compared with the DAPT group (1% vs. 2%; HR, 0.49; 95% CI, 0.33-0.74). The composite of all-cause death, nonfatal myocardial infarction (MI), and nonfatal stroke was 3.9% in both groups. Similarly, the incidences of MI and definite or probable stent thrombosis were not different between groups.

The authors concluded that for post-PCI patients who had completed three months of DAPT with aspirin and ticagrelor, subsequent ticagrelor monotherapy was associated with a lower risk of bleeding compared with continued DAPT, without an increased hazard of ischemic outcomes (including death, MI, and stroke).

■ COMMENTARY

In this large, extremely well-conducted study, the trialists demonstrated a significant bleeding reduction by dropping aspirin after an initial three months of DAPT and continuing monotherapy with the potent antiplatelet agent ticagrelor.

Until recently, the major focus of short DAPT trials has been on ischemic endpoints, primarily MI, stent thrombosis, and mortality. More recently, we have seen increasing recognition that bleeding carries significant hazards, too, and rivals MI for contribution to all-cause death. TWILIGHT is the third major trial this year concerning shortened duration of DAPT post-PCI using P2Y12 inhibitor monotherapy after initial DAPT. SMART-CHOICE and STOPDAPT2 transitioned from DAPT to clopidogrel monotherapy (at three months for SMART and one month for STOPDAPT), with parallel findings of decreased bleeding with similar ischemic event rates in the arms without aspirin. It is entirely possible that the efficacy of prolonged DAPT, as seen in the 2014 DAPT (primarily clopidogrel) and 2015 PEGASUS (ticagrelor) trials, may see benefits primarily from prolonged P2Y12 inhibition.

These recent trials suggest that we may be able to achieve that benefit with less bleeding by dropping aspirin and retaining the P2Y12 inhibitor. Although TWILIGHT patients were required to present with some higher-risk features for ischemic events, the trialists did not focus on acute coronary syndrome (ACS). Fully one-third of the study population was composed of stable elective patients, who in the United States generally would be treated with six months of DAPT. It also is notable that of the ACS patients who were included, more than half were troponin-negative unstable angina patients, and STEMI patients were not included by design. It is unlikely that this trial will be enough to change current thinking regarding use of 12 months of DAPT post-ACS.

One obvious question is why last year's GLOBAL LEADERS trial (*Lancet* 2018;392:940-949), which on the surface featured a similar design, failed to show a similar result. The authors of GLOBAL LEADERS recruited nearly 16,000 patients post-PCI and randomized them (after an initial one-month period of DAPT with aspirin and ticagrelor) to either ticagrelor monotherapy for 23 months or DAPT for 12 months followed by aspirin alone for 12 months. In that trial, there was no apparent benefit of ticagrelor monotherapy in terms of either bleeding or rates of ischemic events.

The TWILIGHT authors noted the double-blind (vs. open label) design of their trial, the enrollment of higher-risk patients, the different duration of therapy studied, and the use of central adjudication of bleeding events (vs. site-reported) as central points contributing to distinct results. In addition, by randomizing only patients

who had successfully completed three months of DAPT, TWILIGHT featured a cleaner design that decreased noise and reduced issues from protocol nonadherence. TWILIGHT suggests that shortening duration of DAPT to three months after PCI with continuation of P2Y12 inhibitor monotherapy is a safe approach that may be considered to decrease bleeding risk. Time will tell whether these data are sufficient to move the needle for revising national guidelines. ■

ABSTRACT & COMMENTARY

Predicting Chemotherapy Cardiotoxicity

By Michael H. Crawford, MD, Editor

SYNOPSIS: Administering trastuzumab after a course of anthracycline therapy for breast cancer can result in cardiac toxicity. Serial echocardiograms in this study showed that a lower initial left ventricular ejection fraction before anthracycline therapy and the amount of decrease in ejection fraction after the anthracycline course are predictive of subsequent trastuzumab cardiac toxicity.

SOURCES: Goel S, et al. Decline in left ventricular ejection fraction following anthracyclines predicts trastuzumab cardiotoxicity. *JACC Heart Fail* 2019;7:795-804.

Ewer MS, Ewer SM. Trastuzumab cardiotoxicity after anthracycline exposure constitutes a complex and clinically important entity. *JACC Heart Fail* 2019;7:805-807.

Trastuzumab therapy is an important chemotherapeutic agent for certain types of breast cancer and can cause dose-dependent, reversible cardiotoxicity (TRC). Current recommendations suggest monitoring cardiac function every three months on this therapy; however, whether findings on cardiac testing predict the development of TRC is unclear.

Goel et al designed this study to determine if baseline left ventricular ejection fraction (LVEF) or changes in LVEF and serum biomarkers or germline genetic polymorphisms can predict the subsequent development of TRC in patients receiving anthracycline-based chemotherapy followed by trastuzumab for breast cancer. This was a multicenter, prospective, observational study from 17 Australian centers. Exclusion criteria were baseline EF < 50%, pregnancy, and prior chemotherapy. LVEF was determined by echo or radionuclide blood pool imaging (MUGA) at baseline, after the completion of anthracycline therapy and every three months during trastuzumab therapy. TRC was defined as the occurrence of any of the following: cardiovascular death; cardiac arrhythmias; ischemia or infarction; New York Heart Association class III or IV heart failure; an asymptomatic decline in EF by > 15% or > 10%, with an absolute value < 50%. Also, plasma troponin and NT-proBNP were measured at the same visits. Baseline DNA was obtained from blood and sequenced. Of 222 patients who met inclusion criteria, five were excluded due to missing data, leaving 217 patients.

TRC developed in 18 patients, most because of a drop in LVEF to < 50%. Baseline characteristics between those who did and did not develop TRC were quite similar. Most TRC events occurred within the first three months after trastuzumab was started. A multivariate analysis showed that TRC was associated with lower baseline EF pre-anthracycline therapy and a greater decline in EF from pre- to post-anthracycline therapy (odds ratio [OR], 3.9 and 7.9, respectively; both $P = 0.0001$). Troponin, NT-proBNP, and genetic polymorphisms were not associated with TRC. The authors concluded that low baseline EF and greater declines in EF on anthracycline therapy were independent predictors of TRC on subsequent trastuzumab therapy.

■ COMMENTARY

Trastuzumab is a monoclonal antibody and was not expected to cause cardiac toxicity. In monotherapy trials, the incidence of cardiac toxicity was 0.4%. However, when combined with anthracycline therapy, more TRC was noted. With concomitant use, it was 16%, but the histology of the myocardium was not what is observed with anthracycline.

Anthracycline can cause myocyte destruction and replacement with fibrosis, leading to permanent damage and life-threatening reductions in LV performance. Trastuzumab is much less malignant, leading some to classify anthracycline toxicity as type 1 and trastuzumab as type 2. Thus, it makes biologic sense that if a patient is recovering from anthracycline toxicity that trastuzumab might potentiate the myocardial injury. Indeed, studies of combination anthracycline plus trastuzumab chemotherapy have shown that the longer the time between anthracycline exposure and trastuzumab administration, the less the cardiotoxicity (3% at

21 days, 0.6% at 89 days). This also fits with the Goel et al study, where most trastuzumab toxicity was observed in the first three months of therapy (in this study, trastuzumab therapy directly followed anthracycline therapy).

One goal of the Goel et al study was to identify low-risk patients who would not need frequent cardiac monitoring when on trastuzumab therapy after a course of anthracycline therapy. Contrary to other smaller studies, Goel et al found no independent predictive value of biomarkers or genetic polymorphisms. They found that LVEF before anthracycline therapy and the change from pre- to post-anthracycline therapy were strongly predictive. Post-anthracycline LVEF was not tested because it certainly would be predictive. Goel et al arrived at a formula for identifying low-risk patients. The formula carried a receiver operating characteristic value of 0.87: [(3× baseline EF) - 4.3] × (EF difference from baseline to post-anthracycline therapy). If this value is > 201%, the risk of TRC is 1.2%, and these patients would be considered low risk. The value of baseline EF has been shown in other studies, but the value of the change in EF is novel and was the most predictive (OR, 7.9).

There were limitations to the study. TRC events were uncommon (8%). Echo and MUGA were used for EF calculations (53% MUGA). This should not have affected the calculation of differences since the two techniques were not used in the same patient, but could have affected the baseline EF calculations. Also, it seems axiomatic that EF values would predict EF, and 14 of 18 patients who developed TRC met only the decrease in EF to < 50% criteria.

Further, LV strain was not evaluated, which some believe is superior to EF. However, the study is of practical value in managing patients treated with both drugs because it puts the EF values we are collecting into clinical perspective. ■

ABSTRACT & COMMENTARY

Planning Therapy for Severe Tricuspid Regurgitation

By Michael H. Crawford, MD, Editor

SYNOPSIS: A retrospective study of moderate to severe secondary tricuspid valve regurgitation showed that right ventricular systolic dysfunction (but not dilatation alone) is predictive of all-cause mortality.

SOURCE: Dietz MF, et al. Prognostic implications of right ventricular remodeling and function in patients with significant secondary tricuspid regurgitation. *Circulation* 2019;140:836-845.

The prognosis of patients with significant tricuspid regurgitation (TR) is closely related to right ventricular (RV) performance. However, the precise measures of RV performance that are indicative of a poor prognosis in significant TR and are possible indications for tricuspid valve (TV) repair or replacement are unknown.

Dietz et al selected patients with moderate to severe secondary TR from their echocardiographic database between 1995 and 2016. Patients with primary TR (prolapse, endocarditis, congenital deformity) were excluded. Key measurements included tricuspid annular (TA) diameter, RV end-diastolic and systolic areas from a focused RV apical view and tricuspid annular plane systolic excursion (TAPSE) from an M-mode recording of the lateral TA from the apical RV view. TR grade was assessed using an integrative approach. Pulmonary artery systolic pressure was estimated from the TR gradient plus the right atrial pressure, which was estimated from imaging the inferior vena cava. Patients were followed for the primary endpoint of all-cause mortality and the secondary endpoint of TV surgery. In the 1,292 patients identified (median age, 71 years; 50% men), four patterns of RV remodeling were defined: 1) no RV dilation or dysfunction (14%), 2) RV dilation but no dysfunction (20%), 3) no RV dilation but RV dysfunction (24%), and 4) RV dilation and dysfunction (43%). Whether the patient had moderate or severe TR was not predictive of the remodeling category. During the median follow-up of 34 months, 40% of the patients died, and only 8% of patients underwent TV surgery (annuloplasty in all). The five-year survival rate was worse in patients with RV dysfunction. (52% in pattern 3, 49% in pattern 4 vs. 70% in pattern 1; $P = 0.002$ and $P < 0.001$, respectively). A multivariate analysis showed that both patterns 3 and 4 (hazard ratio, 1.4 for both) were independent predictors of mortality. The authors concluded that patients with secondary moderate or severe TR and RV systolic dysfunction (but not dilatation alone) experience poor clinical outcomes.

■ COMMENTARY

Data on the natural history of TR is especially welcome now that we have a more viable percutaneous option with the new MitraClip XTR, which includes longer gripping arms. Currently, use in TR is off-label but looks promising. The data presented in this paper suggest that TV repair for severe TR could be entertained for those without RV dysfunction. Interestingly, both American and European guidelines endorse TV repair for symptomatic severe secondary TR if there is no LV or RV systolic dysfunction (class IIa-c). However, this may be a limited number of patients if this series reflects current practice, because two-thirds of their patients with secondary TR showed RV dysfunction and about one-third showed LV systolic dysfunction (ejection fraction < 40%).

Prior studies have shown worse prognosis when TR was associated with RV dilatation and dysfunction, left heart disease, and pulmonary hypertension. The Dietz et al study confirms these findings and adds information on the type of RV remodeling. Also, Dietz et al showed that one can have moderate to severe TR without left heart disease or pulmonary hypertension. Such patients often experienced atrial fibrillation with atrial and tricuspid annular dilatation. Perhaps such patients should be considered for TV repair if RV function is normal. Exact RV functional cutpoints for this decision were not defined in the study and may require more research.

One limitation to this study was the fact it was conducted at one center with a largely homogeneous population and was retrospective. Although the authors could accurately determine the mortality rate, the causes of death were unknown. Also, the study spanned 21 years. Certainly, there were changes in the approach to significant TR during this period. Finally, the authors noted that echo determination of RV size and function is challenging. Cardiac MRI probably would provide more accurate data on RV size and function. However, their data inform future directions in the care of patients with significant secondary TR as well as the type of research needed to flesh out possible future revisions to clinical guidelines. ■

ABSTRACT & COMMENTARY

Safety of Carvedilol for Cocaine Users

By Michael H. Crawford, MD, Editor

SYNOPSIS: The use of beta-blockers in cocaine users is controversial, and there are few data on their use in cocaine-associated heart failure. This prospective, observational, registry study of cocaine-associated heart failure patients showed that carvedilol is safe and effective in such patients.

SOURCES: Banerji D, et al. Carvedilol among patients with heart failure with cocaine-use disorder. *JACC Heart Fail* 2019;7:771-778.

Page RL 2nd, Allen LA. Cocaine, heart failure, and carvedilol: Triangulating the safety of beta-blocker therapy. *JACC Heart Fail* 2019;7:779-781.

Experience with selective beta-adrenergic antagonists in cocaine toxicity has not proven effective, possibly because of unopposed alpha-adrenergic activity. Nonselective beta-blockers, which feature alpha-blocking properties, currently carry a class IIb recommendation for cocaine-associated NSTEMI. However, their use in heart failure with reduced left ventricular ejection fraction (EF) associated with cocaine use is unclear. Banerji et al tested the hypothesis that carvedilol treatment in cocaine use-associated heart failure is safe.

Researchers used a prospective, observational, registry study of all patients admitted with heart failure at one tertiary medical center in 2011. Cocaine use was self-reported or based on urine toxicology. At this hospital, carvedilol was the only beta-blocker administered for cocaine use-associated heart failure. The primary outcome was major adverse cardiac events (MACE), which included 30-day heart failure readmission.

Out of 2,578 patients admitted with acute heart failure, 503 were associated with cocaine use. Among the latter, 404 were treated with carvedilol and 99 with no beta-blockers. At baseline, those receiving carvedilol recorded lower EF rates, heart rate, and NT-proBNP concentrations and exhibited more coronary artery disease.

Over a median follow-up of 19 months, 169 patients experienced a MACE. In a multivariate model, independent predictors of MACE among cocaine users were: history of coronary artery disease, lower EF, elevated pulmonary artery systolic pressure, higher NT-proBNP, lower education level, unemployment,

and less use of standard heart failure medical therapy. Also, MACE rates among those on carvedilol did not differ from those not on carvedilol. Among those with reduced EF (≤ 40%), MACE was lower in those on carvedilol (34% vs. 58%; $P = 0.02$). MACE rates on carvedilol were no different in those with EF > 40%. The authors concluded that carvedilol is effective therapy for those with reduced EF and is safe in cocaine users.

■ COMMENTARY

Despite the "war on drugs," cocaine use is on the rise again in the United States, especially on the East Coast. It is now the most frequently abused drug in patients with heart failure. In this report from a tertiary center in the Bronx, New York, cocaine use was associated with 20% of their acute heart failure admissions. In patients with acute coronary syndromes, there has been a concern that selective beta-blocker use would unleash unopposed alpha-adrenergic stimulation resulting in peripheral and coronary vasoconstriction and lead to poor outcomes.

However, observational studies have not clearly born this out. Current American Heart Association/American College of Cardiology guidelines for patients with NSTEMI or unstable angina state that combined beta- and alpha-blocking agents such as labetalol may be reasonable for treating sinus tachycardia or hypertension in cocaine users as long as a vasodilator is added (class IIb-c). However, little is known about using beta-blockers in patients with heart failure associated with cocaine use. Current guidelines do not address this issue. Thus, this report is of interest. Banerji et al showed that carvedilol was safe, as the overall results in those who received the drug vs. those who did not were similar. As expected, those who recorded an LVEF ≤ 40% performed better on carvedilol than those who did not take the drug. The results also are biologically plausible since carvedilol blocks alpha- and beta-adrenergic receptors. Although carvedilol use was based on prescribing information only, the lower resting heart rates in those on carvedilol supports that the drug was taken by the patients. Also, the lower NT-proBNP levels in those on carvedilol suggests that cardiac chamber wall tension was reduced. Interestingly, the type of cocaine or the frequency of use did not seem to influence the results.

This study only evaluated carvedilol because that was the only agent used at this institution. Labetalol has similar properties to carvedilol, but has a much higher dosage range (up to 2,400 mg), which will make selecting the optimal dose difficult. Also, carvedilol is lipophilic, and penetration into the brain may reduce central sympathetic output as well. In addition, carvedilol is currently less expensive than labetalol.

There are limitations to this study, starting with the selection bias and unmeasured confounders that plague all observational studies. Also, those not given beta-blockers were a small group and were sicker with more advanced disease. At this point, the safety of using carvedilol in selected patients probably is valid, but clearly more studies are warranted for this growing problem. ■

ABSTRACT & COMMENTARY

Cardiac Arrest in Takotsubo Syndrome

By Michael H. Crawford, MD, Editor

SYNOPSIS: Investigators sought to determine whether secondary prevention interventions could reduce the mortality rate of takotsubo patients with cardiac arrest.

SOURCES: Gili S, et al. Cardiac arrest in takotsubo syndrome: Results from the InterTak Registry. *Eur Heart J* 2019;40:2142-2151.

Wittstein IS. Cardiac arrest and takotsubo syndrome. *Eur Heart J* 2019;40:2152-2154.

Although usually benign, takotsubo syndrome (TS) can cause life-threatening complications, but little is known about the frequency and outcomes of cardiac arrest (CA) in TS.

Researchers from the International Takotsubo (InterTAK) Registry interrogated this multicenter, prospective registry of TS patients from 2011 through 2017 for patients with CA and known underlying rhythm. Of the 2,098 patients available at the time, 124 met the inclusion criteria. Baseline characteristics showed that CA patients were younger and more often men compared to the rest of the patients. On admission, study subjects presented with lower left ventricular ejection fraction and more often were in atrial fibrillation (21% vs. 6%; $P < 0.001$). CA was the presentation of TS in 82%, and 18% developed CA during the acute phase of TS. In the CA at presentation group, 57% had ventricular fibrillation or tachycardia (VF/VT), while 74% of those who developed CA in the acute phase exhibited asystole or pulseless electrical activity (PEA).

Patients with CA died more often at 60 days (40% vs. 4%; $P < 0.001$) and five years (69% vs. 17%; $P < 0.001$). The multivariate adjusted predictors of 60-day mortality were T wave inversion on ECG, intracranial hemorrhage, and male sex.

The authors concluded that CA was not uncommon in TS, is associated with higher short- and long-term mortality, and can be predicted by clinical and ECG parameters.

■ COMMENTARY

Today, TS is recognized more often since we are treating more patients with suspected acute coronary syndrome for left heart catheterization. Also, the characteristic regional wall motion patterns are becoming more familiar on echocardiography. Although generally considered a low-risk condition because the wall motion abnormalities usually are reversible, in-hospital mortality is similar to acute myocardial infarction.

This investigation, based on the InterTAK Registry, showed that CA occurred in 6% of TS patients, and CA that occurred in hospital carried a mortality rate of 35%. T wave inversion on ECG and the presence of intracranial hemorrhage were independent predictors of mortality. Indeed, CA was more common in TS patients with physical triggers rather than emotional ones.

Since mortality occurred more often in those with physical conditions triggering TS, this may be due to the underlying disease or other comorbidities in these patients. However, late mortality was six-fold higher in post-CA patients compared to TS patients without CA. It is difficult to understand how physical conditions would increase five-year mortality so markedly. This raises the question of whether TS patients who go into CA should go home with a defibrillator vest or receive an implantable cardioverter defibrillator (ICD).

About 80% of CA patients experienced their arrest at presentation and usually were in VF/VT. In the one-fifth who developed CA after admission for TS, it usually was because of PEA or asystole, which suggests they presented with severe myocardial dysfunction. Consequently, the latter patients may not benefit from an ICD. Since the median time to CA was one day, TS patients should be monitored (at a minimum) for 48-72 hours.

What to do after that is unclear, as initial anecdotal experience with ICDs has been disappointing. Further research will be required to determine the best secondary prevention technique for these challenging patients with TS and CA. ■

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CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. **A recent post-percutaneous coronary intervention trial comparing ticagrelor plus aspirin for three months followed by either continued dual therapy or ticagrelor alone for nine more months showed that ticagrelor alone decreased:**

   a. major bleeding events.

   b. all-cause death.

   c. non-fatal myocardial infarction.

   d. non-fatal stroke.

2. **Among patients with cocaine use-associated heart failure, which condition predicts reduced adverse cardiac events with carvedilol therapy?**

   a. Elevated pulmonary artery systolic pressure

   b. History of coronary artery disease

   c. Left ventricular ejection fraction (LVEF) < 40%

   d. Elevated NT-proBNP

3. **Which predicts trastuzumab cardiac toxicity following a course of anthracycline therapy for breast cancer?**

   a. A large drop in LVEF on anthracycline therapy

   b. Troponin level

   c. Specific genetic polymorphisms

   d. Normal baseline LVEF

4. **Which is true concerning cardiac arrest in takotsubo syndrome?**

   a. It occurs in 5-10% of patients.

   b. It usually occurs five to seven days after hospital admission.

   c. It is usually due to pulseless electrical activity arrest or asystole.

   d. It occurs mainly in women.

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications, of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.